



King's Research Portal

DOI:

[10.3233/JPD-150656](https://doi.org/10.3233/JPD-150656)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Fauser, M., Löhle, M., Ebersbach, G., Odin, P., Fuchs, G., Jost, W. H., Ray Chaudhuri, K., Koch, R., & Storch, A. (2015). Intraindividual Variability of Nonmotor Fluctuations in Advanced Parkinson's Disease. *Journal of Parkinson's Disease*, 5, 737-741. <https://doi.org/10.3233/JPD-150656>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Short Communication

Intraindividual Variability of Nonmotor Fluctuations in Advanced Parkinson's Disease

Mareike Fauser^a, Matthias Löhle^{a,b}, Georg Ebersbach^c, Per Odin^{d,e}, Gerd Fuchs^f, Wolfgang H. Jost^f, K. Ray Chaudhuri^g, Rainer Koch^h, NoMoFlu-PD study group and Alexander Storch^{a,b,i,*}

^a*Division of Neurodegenerative Diseases, Department of Neurology, Technische Universität Dresden, Dresden, Germany*

^b*Department of Neurology, University of Rostock, Rostock, Germany*

^c*Movement Disorders Clinic, Beelitz-Heilstätten, Germany*

^d*Department of Neurology, Klinikum Bremerhaven, Bremerhaven, Germany*

^e*Department of Neurology, University Hospital, Lund, Sweden*

^f*Parkinson Clinic Wolfach, Wolfach, Germany*

^g*National Parkinson Foundation Centre of Excellence, Kings College Hospital and Kings College London and Biomedical Research Centre, Kings College London, UK*

^h*Department of Medical Informatics and Biometry, Technische Universität Dresden, Dresden, Germany*

ⁱ*German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany*

Abstract. Nonmotor symptoms (NMS) fluctuate in conjunction with motor oscillations in advanced Parkinson's disease (PD), though little is known about the variability of NMS fluctuations in individual patients. We aimed to assess within-patient variability in frequency and severity of NMS during a series of five patient-perceived motor On and Off periods in 38 fluctuating PD patients from the multicenter NonMotorFluctuations in PD study using a visual analogue scale. NMS frequency and severity appeared moderately variable in both motor states within individual patients. Symptom severity ranges between motor states showed high variability and were larger in motor Off states for most NMS.

Keywords: Nonmotor symptoms, nonmotor fluctuations, intraindividual variability, Parkinson's disease, NMS domains

INTRODUCTION

Nonmotor symptoms (NMS) are reported in the majority of Parkinson's disease (PD) patients and have strong impact on health-related quality of life (hr-QoL) [1]. Fluctuations of NMS can occur with oscillations

in response to dopaminergic medication [2–4] and are present in up to 100% of fluctuating PD patients [3, 5]. This study complements preceding reports of the NonMotor Fluctuations in PD (NoMoFlu-PD) study, a multicenter cross-sectional study to assess NMS fluctuations (NMF) and their correlation with motor fluctuations and hr-QoL [6, 7], which used semi-structured interviews in combination with visual analogue scales (VAS) and VAS-based home diaries to characterize NMF in relation to motor states. We

*Correspondence to: Alexander Storch, M.D., Department of Neurology, University of Rostock, Gehlsheimer Strasse 20, 18147 Rostock, Germany. Tel.: +49 381 494 9510; Fax: +49 381 494 9512; E-mail: alexander.storch@med.uni-rostock.de.

found complex heterogeneous patterns of NMFs with particularly frequent and severe fluctuations in psychiatric NMS compared to other NMS domains [6, 7]. However, it remains unclear whether and how NMF vary in an individual subject. The repeated evaluation of ten key NMS over five motor On and five Off periods reported in this manuscript allowed us to estimate the intraindividual (within-patient) stability of NMF. The present analyses thus aim to investigate intraindividual NMS variability of symptom frequency and severity between multiple motor On/Off states based on repeated home diary assessments in fluctuating PD.

SUBJECTS AND METHODS

The study population and assessments have been described elsewhere [6]. In brief, PD patients of all ages and disease severities were included in the NoMoFlu-PD study, if they experienced documented motor fluctuations and in addition did not show any signs of atypical parkinsonism, psychosis, dementia or other relevant conditions interfering with the study protocol. Subjects rated a total of ten NMS (Table 1) during five self-perceived motor On and Off states at home as “present” or “absent” and subsequently the NMS severity using a visual analogue scale (VAS) with a symptom range from 0 (not present) to 100 (maximum symptom intensity). During the initial study visit, patients were trained in how to use a visual analogue scale and their diaries. In addition, the study visit included a levodopa challenge test, so patients were asked to arrive in the outpatient clinic after a 12 hour medication withdrawal [6]. During the visit, patients experienced both a defined motor On and Off state and were asked to complete their home diaries while experiencing similar motor states.

Statistical comparisons between motor states and NMS intensity ranges or patterns, respectively, were calculated using Wilcoxon rank test, McNemar test, Student's paired and unpaired *t*-test, χ^2 , Fisher's exact test, and Friedman non-parametric repeated-measure ANOVA as appropriate. In addition, we calculated Mahalanobis distances (MD), a measure of the distance between individual patients' NMS severity ranges and mean NMS ranges across all the NMS. If not stated otherwise, data are displayed as mean \pm standard deviation (SD), absolute numbers or numbers (%). Two-tailed $P < 0.05$ were deemed statistically significant. Due to the explorative character of the study, α adjustment of *P*-values has not been carried out.

RESULTS

Demographic characteristics of the overall NoMoFlu-PD study cohort have been reported previously [6]. Complete home diary datasets were available from 38 (38%) patients (24 men (63%); mean age \pm SD: 65.6 ± 8.2 years; disease duration: 10.3 ± 7.0 years; Hoehn and Yahr stage in On: 2.4 ± 0.9 and Off state: 3.1 ± 1.0 ; $P < 0.0001$ [Wilcoxon test]; UPDRSIII motor score in On: 15.3 ± 11.9 and Off: 31.1 ± 12.0 ; $P < 0.0001$ [paired *t*-test]). Patients with complete home diary datasets had younger age, shorter disease duration and milder PD symptoms compared to patients without complete home diary data (see Supplementary Table 1 for complete statistics). All subsequent analyses were performed for the former patient cohort in order to prevent bias due to skewed adherence to diary records. Most of the diaries were completed in the morning hours before 12:00 am for both motor states (medians [maximal interquartile ranges]: 9:30 to 11:30 [8:30–14:30] for the five On and 8:30 to 11:30 [7:00–16:00] for the five Off states) with no significant differences between the various motor states ($P > 0.05$; Friedman ANOVA).

For the assessment of intraindividual variability of NMF, diary data were dichotomized to assign patients to one of two groups within each motor state: “instable” fluctuating patients reported a respective NMS within 1–4 of 5 assessments of a given motor state, whilst “stable” fluctuating subjects presented with a specific NMS during either all or none of the investigated motor state. The percentage of instable fluctuating PD patients was used to assess NMS recurrence in the respective motor state (Table 1). We found a significantly higher proportion of instable NMS fluctuators within motor Off states solely for depression ($P = 0.007$), anxiety ($P = 0.031$) and bladder urgency ($P = 0.0049$). All other NMS did not differ significantly between motor states. We did not detect any differences of demographic and clinical characteristics between stable and instable NMS fluctuators.

To further characterize NMS presentation in individual patients, we analyzed NMF patterns within both motor states. Patterns were defined according to the number of presentation of individual NMS over the total of five motor states ranging from 0/5 (symptom absent in all five assessments) to 5/5 (symptom present in all five explorations). All NMS except problems with concentration/attention, bladder urgency, excessive sweating and dysphagia demonstrated a significantly different distribution of NMF between the

two motor states with a shift towards a more unstable and more frequent occurrence of NMS in motor Off state compared to motor On state (Supplementary Table 2).

Next, we assessed the variability of severities of these ten NMS between different On states and different Off states on the individual subject level. We therefore used the range of home diary VAS scores from a total of five self-perceived motor On as well as Off states in each individual as a measure of motor symptoms and NMS severity variability with higher ranges representing higher variability (Table 2). Although the motor function was rated worse in Off compared to On state ($63 \pm 17\%$ versus $39 \pm 22\%$ on VAS, $P < 0.001$, Wilcoxon test) [6], the intraindividual variability of motor dysfunction between the motor On and Off states did not show significant

differences. Except for dysphagia, all NMS demonstrated a significantly higher intraindividual variability (higher ranges) in symptom severity during motor Off states. Using the Mahalanobis distance (MD) as a multidimensional measure of data distribution of all NMS severity ranges within each individual subject, we found that intraindividual NMS severity ranges were not significantly different between motor On and Off states ($P = 0.392$). Similar results were obtained for both motor states when using only morning ratings from before 12:00 am (not shown). Normalization of NMS severity to motor function of the respective motor state led to increased intraindividual severity variability of all NMS on both motor states (Supplementary Table 3). We did not detect differences between the patients with complete and incomplete diary.

Table 1
Instability of nonmotor symptoms during a series of motor On and Off states

Nonmotor domain	Nonmotor symptom	Instable NMS fluctuations ^a (% of motor fluctuating subjects)		<i>P</i> value ^b
		Motor On state	Motor Off state	
<i>Psychiatric NMS</i>	Depression	6 (15.8%)	17 (44.7%)	0.007
	Anxiety	8 (21.1%)	18 (47.3%)	0.031
	Concentration/attention	10 (26.3%)	12 (31.6%)	0.791
	Fatigue	20 (52.6%)	14 (36.8%)	0.238
<i>Autonomic NMS</i>	Bladder urgency	9 (23.7%)	18 (47.4%)	0.049
	Excessive sweating	11 (28.9%)	14 (36.8%)	0.629
	Dizziness	11 (28.9%)	10 (26.3%)	1.000
<i>Sensory NMS</i>	Pain	14 (36.8%)	9 (23.7%)	0.267
<i>Miscellaneous</i>	Dysphagia	5 (13.2%)	13 (34.2%)	0.057
	Inner restlessness	11 (28.9%)	15 (39.5%)	0.344

^a Instable patients are defined as fluctuating patients reporting a respective NMS within 1–4 of 5 assessments of a given motor state. ^b *P* values are from McNemar test.

Table 2
Intraindividual variability of motor and nonmotor symptom severities between different motor On and different Off states^a

Motor function/ NMS domain	Nonmotor symptom	Motor On state			Motor Off state			<i>P</i> value ^b
		Mean \pm SD range	Median range	Min-Max	Mean \pm SD range	Median range	Min-Max	
<i>Motor function</i>		23.7 \pm 22.1	20	0–80	20.1 \pm 15.5	20	0–60	0.341
<i>Psychiatric NMS</i>	<i>Depression</i>	8.4 \pm 14.8***	0	0–60	34.3 \pm 30.6*	30	0–100	<0.001
	<i>Anxiety</i>	5.7 \pm 11.9**	0	0–50	27.9 \pm 29.1**	20	0–90	<0.001
	<i>Concentration/attention</i>	5.3 \pm 9.7***	0	0–40	17.6 \pm 23.7	5	0–80	0.001
	<i>Fatigue</i>	12.0 \pm 18.0*	0	0–60	32.0 \pm 26.3**	30	0–90	<0.001
<i>Autonomic NMS</i>	<i>Bladder urgency</i>	11.7 \pm 18.5*	0	0–70	27.8 \pm 30.8	20	0–80	0.006
	<i>Excessive sweating</i>	13.7 \pm 23.6*	0	0–70	20.4 \pm 30.8	0	0–100	0.047
	<i>Dizziness</i>	8.8 \pm 17.5**	0	0–70	18.7 \pm 24.5	0	0–80	0.005
<i>Sensory NMS</i>	<i>Pain</i>	16.6 \pm 22.7	0	0–70	31.1 \pm 29.9*	30	0–100	0.006
<i>Miscellaneous</i>	<i>Dysphagia</i>	3.7 \pm 10.2***	0	0–50	5.0 \pm 9.8***	0	0–40	0.154
	<i>Inner restlessness</i>	18.4 \pm 21.2	0	0–70	30.5 \pm 31.0*	25	0–100	0.017
Mahalanobis distance		9.4 \pm 4.2	9.8	2.8–17.4	10.3 \pm 4.3	10.6	3.1–19.2	0.392

^a Displayed are the ranges of home diary VAS scores from a total of five self-perceived motor On as well as Off states in each individual as a measure of motor symptom and NMS severity variability. Higher ranges represent higher variability. The Mahalanobis distance was calculated as a multidimensional measure of data distribution of all NMS severity ranges within each individual subject. *represents $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ when compared to motor function. ^b *P* values are from Wilcoxon test.

DISCUSSION

Although severity and variability of NMF and their correlation with motor complications have been described before [3, 6], there are no reports on intraindividual variability of NMS presentations within defined motor states. By using a systematic assessment of key NMS during a series of five motor On and five Off periods [6], we detected a moderate intraindividual variability of NMS frequencies and severities between multiple motor On and Off states, with 13–52% instable fluctuators for motor On and 24–47% instable fluctuators for motor Off state. Frequencies of instable fluctuators were higher for motor Off compared to motor On states for anxiety, depression and bladder urgency, but not for other NMS.

The factors influencing intraindividual NMF variability remain largely enigmatic. Similar to the findings in group analyses showing no or only weak correlations of NMF with motor function or disease state and no associations with demographic data [6–9], we did not detect any associations of intraindividual NMF instability and demographic or clinical characteristics. Indeed, normalization of NMS severity to motor function for each motor On or Off state even increases NMF variability in the present study. NMF variability in the present study seems to be largely independent from circadian influences, since the ratings were performed mainly in the morning and no differences in the time of rating were detected between the various motor states. Future studies systematically investigating the timing of NMS and NMF are thus warranted to further characterize the circadian rhythm of NMS and their fluctuations.

Several limitations of the present study need to be addressed. First, NMS in our study were rated during self-perceived motor states, hence we cannot exclude that these motor states were different from investigator-controlled On and Off states. Nevertheless, this study reflects highly relevant clinical data on everyday life of PD patients since self-reported outcomes are more likely to provide a realistic impression of individual NMS burden. Second, complete diary datasets were available from only 38% of patients, most likely due to diary fatigue or higher stress burden by diary entries in the older and more advanced patients [10]. Although we did not detect any relevant differences between completers and non-completers, our data should be interpreted only for the younger and less advanced fluctuating PD population (see Supplementary Table 1). Third, we confined our report to motor On state without distinguishing between “motor On” and “On with

dyskinesias” [6], since most patients have difficulties judging their hyperkinetic conditions [11], which are known to influence at least some NMS, such as, e.g., dysphagia [12] and pain [5]. The addition of a caregiver diary to adequately evaluate motor states might thus be of additional benefit in future studies. Fourth, we used the range of VAS values from 5 different time points as an aggregate value for the intraindividual variability of NMS. Although the test-retest reliability of VAS is reported to be high for most symptoms [13–15], we cannot exclude bias due to limited intra-rater agreement for the severity analyses of some NMS.

Our study reports moderate intraindividual variability in NMF with respect to defined motor states. Psychiatric NMF were found to be particularly instable concerning symptom frequency and severity, particularly in motor Off states. The variability and thus unpredictability of NMF might contribute to the huge impact of NMF on hr-QoL [3, 6]. Further research on NMFs in PD therefore needs to address NMS on a longitudinal basis to fully encompass their impact on hr-QoL and to draw conclusions for necessary treatment adjustments such as continuous dopaminergic stimulation.

ACKNOWLEDGMENTS

We acknowledge all collaborators of NoMoFlu-PD study group and the international Parkinson's disease non motor group who have contributed to the concept of this work. The NoMoFlu-PD Study Group consists of the following structure:

NoMoFlu PD steering committee: K. Ray Chaudhuri, National Parkinson Foundation Centre of Excellence, Kings College Hospital and Kings College London and Biomedical Research Centre, Kings College London, UK; Georg Ebersbach, Movement Disorders Clinic, Beelitz-Heilstätten, Germany; Gerd Fuchs, Parkinson Clinic Wolfach, Wolfach, Germany; Wolfgang H. Jost, Dept. of Neurology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany; Per Odin, Dept. of Neurology, Klinikum Bremerhaven, Bremerhaven, Germany; Alexander Storch, Division of Neurodegenerative Diseases, Dept. of Neurology, Dresden University of Technology, and German Centre for Neurodegenerative Diseases (DZNE), Research Site Dresden, Dresden, Germany.

Participating centers and investigators: Division of Neurodegenerative Diseases, Dept. of Neurology, Dresden University of Technology, and DZNE, German Centre for Neurodegenerative Diseases,

Research Site Dresden, Dresden, Germany (Drs. Storch, Schneider, Wolz, Klingelhöfer, Fauser, Reichmann; Melzer, Schürwald; Bosredon, Schmidt, A. Wolz [study nurses]); Movement Disorders Clinic, Beelitz-Heilstätten, Germany (Drs. Nebe, Ebersbach); Dept. of Neurology, Klinikum Bremerhaven, Bremerhaven, Germany (Gies, Drs. Odin, Mahler); Parkinson Clinic Wolfach, Wolfach, Germany (Dr. Fuchs); Dept. of Neurology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany (Dr. Jost).

Statistical analysis: Dr. Koch (Dept. of Biometrics and Medical Informatics, Dresden University of Technology); Drs. Storch, Schneider (Div. of Neurodegenerative Diseases, Dept. of Neurology, Dresden University of Technology). Drs. Storch, Schneider and Koch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: Study concept and design (Drs. Storch, Odin, Fuchs, Jost, Ebersbach); acquisition of data (Drs. Storch, Odin, Jost, Fuchs, Ebersbach); analyzing of data (Drs. Storch, Koch); interpretation of data (Drs. Storch, Odin, Fuchs, Jost, Chaudhuri, Ebersbach); drafting the manuscript (Drs. Storch, Fauser); important critical revision of the manuscript (Drs. Löhle, Odin, Fuchs, Jost, Chaudhuri, Koch).

This study was supported in part by an unrestricted research grant from Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany. The financial sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had the final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary table is available in the electronic version of this article: <http://dx.doi.org/10.3233/JPD-150656>.

REFERENCES

- [1] Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, & Chaudhuri KR (2011) The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord*, **26**, 399-406.
- [2] Hillen ME, & Sage JI (1996) Nonmotor fluctuations in patients with Parkinson's disease. *Neurology*, **47**, 1180-1183.
- [3] Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, & Cherif AA (2002) Nonmotor fluctuations in Parkinson's disease: Frequent and disabling. *Neurology*, **59**, 408-413.
- [4] Stacy MA, Murphy JM, Greeley DR, Stewart RM, Murck H, & Meng X (2008) The sensitivity and specificity of the 9-item Wearing-off Questionnaire. *Parkinsonism Relat Disord*, **14**, 205-212.
- [5] Bayulkem K, & Lopez G (2011) Clinical approach to nonmotor sensory fluctuations in Parkinson's disease. *J Neurol Sci*, **310**, 82-85.
- [6] Storch A, Schneider CB, Wolz M, Sturwald Y, Nebe A, Odin P, Mahler A, Fuchs G, Jost WH, Chaudhuri KR, Koch R, Reichmann H, & Ebersbach G (2013) Nonmotor fluctuations in Parkinson disease: Severity and correlation with motor complications. *Neurology*, **80**, 800-809.
- [7] Storch A, Schneider CB, Klingelhöfer L, Odin P, Fuchs G, Jost WH, Martinez-Martin P, Koch R, Reichmann H, Chaudhuri KR, group N-Ps, Ebersbach G (2015) Quantitative assessment of nonmotor fluctuations in Parkinson's disease using the Non Motor Symptoms Scale (NMSS). *J Neural Transm*, **122**, 1673-1684.
- [8] Seki M, Takahashi K, Uematsu D, Mihara B, Morita Y, Isozumi K, Ohta K, Muramatsu K, Shirai T, Nogawa S, Gotoh J, Yamaguchi K, Tomita Y, Yasutomi D, Nihei Y, Iwasawa S, & Suzuki N (2013) Clinical features and varieties of non-motor fluctuations in Parkinson's disease: A Japanese multicenter study. *Parkinsonism Relat Disord*, **19**, 104-108.
- [9] Gunal DI, Nurichalichi K, Tuncer N, Bekiroglu N, & Aktan S (2002) The clinical profile of nonmotor fluctuations in Parkinson's disease patients. *Can J Neurol Sci*, **29**, 61-64.
- [10] Papapetropoulos SS (2012) Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Ther*, **18**, 380-387.
- [11] Pietracupa S, Fasano A, Fabbrini G, Sarchioto M, Bloise M, Latorre A, Altieri M, Bologna M, & Berardelli A (2013) Poor self-awareness of levodopa-induced dyskinesias in Parkinson's disease: Clinical features and mechanisms. *Parkinsonism Relat Disord*, **19**, 1004-1008.
- [12] Monte FS, da Silva-Junior FP, Braga-Neto P, Nobre e Souza MA, & de Bruin VM (2005) Swallowing abnormalities and dyskinesia in Parkinson's disease. *Mov Disord*, **20**, 457-462.
- [13] Fahndrich E, & Linden M (1982) [Reliability and validity of the Visual Analogue Scale (VAS) (author's transl)]. *Pharmacopsychiatria*, **15**, 90-94.
- [14] Lee KA, Hicks G, & Nino-Murcia G (1991) Validity and reliability of a scale to assess fatigue. *Psychiatry Res*, **36**, 291-298.
- [15] Miller MD, & Ferris DG (1993) Measurement of subjective phenomena in primary care research: The Visual Analogue Scale. *Fam Pract Res J*, **13**, 15-24.